REMARKS

Claims 20-35 are pending in the application. Claims 1-19 have been cancelled.

New claims 20-35 do not incorporate new matter. Support for the subject matter of each of the new claims is found at least in the specification at page 4, lines 5-6 and 28-29, page 8, lines 24-25 and in claims 1-12 as originally filed.

In the Office Action, the Examiner has rejected claims 13-19 under 35 U.S.C. § 103 as being unpatentable over:

(i) U.S. Patent No. 5,482,706 of Igari, *et al.* ("Igari");

(ii) U.S. Patent No. 5,589,453 of Greve, *et al.* ("Greve");

(iii) U.S. Patent No. 5,730,983 of Wegner, *et al.* ("Wegner");

(iv) U.S. Patent No. 5,422,907 of Gwaltney, *et al.* ("Gwaltney");

(v) U.S. Patent No. 5,690,954 of Illum ("Illum '954");

(vi) U.S. Patent No 5,707,644 of Illum ("Illum '644"); and

(vii) Kublik, *et al.*, *Eur. J. Pharm. Biopharm.* 39:192-196, 1993 ("Kublik").

Applying these references, the Examiner has made three combinations which he asserts render claims 13-19 to be obvious:

- The combination of Igari and Greve, taken in view of Wegner, Gwaltney, Illum '954, Illum '644, and Kublik;
- The combination of Igari alone taken in view of Wegner, Gwaltney, Illum '954, Illum '644, and Kublik; and
- The combination of Greve alone taken in view of Wegner, Gwaltney, Illum '954, Illum '644, and Kublik.

As noted above, claims 13-19 have been cancelled. However, the applicant traverses the rejection, should it be applied to any of the new claims 20-34.

The Cited Prior Art – Summary of Its Teachings

Detailed summaries of each of the cited references have been provided by the applicant in the Amendment, filed April 10, 2003, and are incorporated herein by reference. As discussed previously, Igari teaches dispersion of a physiological peptide or protein, such as ICAM-1, into a

pharmaceutically acceptable base or vehicle. Igari does not teach dispersion of the physiologically active peptide or protein in a chitosan solution, nor does it teach the preparation of microspheres of starch, chitosan, gelatin, gellan, hyaluronic acid or alginate into which ICAM-1 is incorporated. Moreover, as the Examiner has previously noted, Igari does not teach use of ICAM-1 to inhibit rhinovirus infections.

Greve merely discloses that a water soluble preparation of the human rhinovirus major receptor exhibits the property of binding to human rhinovirus capsids, and can reduce the infectivity of the virus. Greve states in the abstract that the particular human rhinovirus receptor protein being studied has been determined to be ICAM-1, although no primary amino acid sequences are disclosed in Greve. All examples in Greve are conducted *in vitro*; none of the Greve preparations is incorporated into a pharmaceutical composition, nor is it administered to a patient. In addition, the Examiner himself concedes that Greve does not disclose a composition including a bioadhesive, such as the chitosan solution or the microspheres recited in the claims.

Wegner specifically teaches administration of agents that prevent or exhibit cellular adhesion to the lung endothelia (cells of the lungs). Wegner does not teach use of ICAM-1 and a chitosan solution. It specifically does not teach or suggest that microspheres can be formulated from chitosan, gelatin, gellan, starch, hyaluronic acid and alginate. Most notably, it does not teach adherence of any of the compositions of Wenger to the mucosal surface and/or epithelia of the nasal cavity.

Gwaltney discloses a systemically-administered composition including antiviral agents and an anti-inflammatory compound such as anti ICAM-1 antibodies and synthetic ICAM-1. Gwaltney does not teach or suggest administration of this composition to the nasal cavity, nor does it teach or suggest incorporation or encapsulation of the anti-viral agent and/or anti-inflammatory compound into a microsphere of any material or use of a chitosan solution.

Illum '954 and Illum '644 (collectively "the Illum references") teach use of a drug delivery composition containing microspheres that include starch, gelatin, dextran, collagen, and gellan gum for use in the systemic administration of drugs to a human patient (Illum '644). Neither discloses use of a composition containing ICAM-1. The Illum references are directed to systemic drug delivery through the surfaces lining the nasal cavity. They do not address compositions that are designed intranasally administer ICAM-1 to the nasal cavity by adhering it to the surfaces of the cavity.

Kublik provides a general teaching concerning the use of nasal applications of drug compositions for systemic delivery. Kublik provides a rheological characterization of a solution for nasal administrations containing Gelrite™ (gellan gum) and hydroxyl methylcellulose. However, Kublik teaches that the rheological properties of a given solution do not necessarily bear a relationship to the viscosity and/or bioavailability of nasally administered polymer solutions. Moreover, Kublik does not disclose composition containing chitosan in any form nor does it disclose use of a bioadhesive that is a microsphere comprising chitosan, gelatin, starch hyaluronic acid, alginate, and/or gellan.

No Combination of the Cited Reference Renders the Claimed Invention Obvious

First, with respect to the Examiner's comments in Paper No. 14, the applicant submits that no attempt has been or was made to "argue the references individually." The applicant's preliminary discussion of each of the individual references was provided merely to highlight the Examiner's failure to meet the legal standard of a *prima facie* case of obviousness for lack of motivation, lack of a reasonable expectation of success, and lack of disclosure of the claim elements in any of the cited references. Logic and legal principles dictate that if the same claim element(s) or motivation is absent from each individual cited art reference, the mere combination of these deficient references does not remedy the insufficiencies. Thus, individual discussions of all references are necessary.

In the present case, no combination of the six prior art references cited by the Examiner establishes a *prima facie* case of obviousness. First, no combination of the reference teaches or suggests all element of the invention. With respect to the composition of the invention, the combination of the references lacks disclosure of : (i) a composition that includes a chitosan solution and ICAM-1 (claims 20, 21), and (ii) a composition that includes a plurality of microspheres of the recited materials and ICAM-1 (claims 23-25) and (iii) a ICAM-1 composition that is adapted to be adhered to the epithelia and/or mucosal surface of the nasal cavity. With respect to the method claims of the invention, any combination of the cited prior art references lacks disclosure of: (i) a method of treating a viral infection affecting the nasal cavity including adhering an antivirally effective amount of the recited composition to the epithelia and/or mucosal surface of the nasal cavity (claim 26-35); (ii) using a ICAM-1 composition that includes the recited bioadhesives (chitosan solution and microspheres of specific materials)

(claims 26-35); and (iii) a method of improving the retention of an ICAM-1 composition in the nasal cavity (claim 34 and 35).

Igari and Greve, the 'primary' references upon which the Examiner relies, do not teach use of a chitosan solution in their disclosed compositions. The base materials in Igari are taught as being formed into solid, not liquid, dosage forms. Moreover, no disclosure of microspheres of the recited materials (starch, chitosan, gelatin, gellan, hyaluronic acid or alginate) is provided. Moreover, Igari is lacking any disclosure of microspheres made of the recited materials and adhesives of the composition to the epithelia and/or mucosal surface of the nasal cavity.

Greve is a "basic science" reference in that no specific practical applications, pharmaceutical or otherwise, are taught or suggested. Greve does not address in any manner whether the ICAM-1 used in the basic science experiments can be formulated into any excipient or carrier substance for administration to any multicellular living being for therapeutic purposes. Greve does not discuss use of a chitosan solution. Indeed, Greve does not even teach or suggest that the ICAM-1 disclosed therein can be formulated into any type of pharmaceutical composition or chitosan solution, as the Examiner himself has conceded Greve does not discuss use of the microspheres as recited. Greve does not teach or suggest methods for administering ICAM-1 to the nasal cavity so that the retention of the ICAM-1 in the nasal cavity shall be improved.

None of the other references as combined by the Examiner can fill these voids in the disclosures of Igari and Greve. Neither Wenger, Gwaltney, the Illum references, or Kublik discloses a chitosan solution, and this deficiency of claim element in the Examiner's combination remains unremedied. None of the remaining references teaches adherence of the ICAM-1 composition to the epithelia and/or mucosal surface of the nasal cavity or use of microspheres of the recited materials (starch, chitosan, gelatin, hyaluronic acid, alginate, or gellan) and ICAM-1. Wenger does not teach used of a chitosan solution or microspheres of the recited materials. Moreover, Wenger teach application of the Wenger composition to the epithelia of the lungs, not adhering the composition to the epithelia and/or mucosal surface of the nasal cavity.

Similarly the disclosures of Gwaltney, the Illum references and Kublik lack a teaching of an ICAM-1 composition including a chitosan solution. It additionally does not disclose adherence of the composition to the epithelia and/or mucosal surfaces of the nasal cavity.

Second, the Examiner has failed to demonstrate that person of skill would have been motivated to make the combination suggested by the Examiner. A person of skill in the art would have had no motivation in the art to make any of the combinations suggested by the Examiner, nor would he have had a reasonable expectation that such combination would give rise to a successful composition for nasal administration of ICAM-1 to the nasal cavity. Greve makes no disclosure of any pharmaceutical composition or *in vivo* pharmaceutical use of ICAM-1. None of the remaining references cited by the Examiner addresses the difficulty of preparing a composition that allows for the administration of an active agent to the nasal cavity. Gwaltney, the Illum references, and Kublik each teach compositions that are adapted for transport of the selected active agent via the nasal route into the bloodstream. Wenger is expressly designed to administer the ICAM-1-containing composition to the endothelial cells of the lung, via any feasible administration route, including oral or nasal routes. Accordingly, a person seeking to prepare a composition which is adapted to deliver an antivirally effective amount of ICAM-1 to the nasal cavity would not rely upon, or combine teachings of, references directed to compositions which facilitate systemic administration of a drug or active agent. Further, given these teachings, it is unlikely that a person of skill would have had a reasonable expectation of success.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the Examiner's § 103 rejection has been addressed. Accordingly, reconsideration and allowance of new claims 20-35 are respectfully requested.

Respectfully submitted,

PETER WATTS

5 February 2004 By: Kristyne A. Bullock
(Date)

KRISTYNE A. BULLOCK
Registration No. 42,371
AKIN GUMP STRAUSS HAUER & FELD LLP
One Commerce Square
2005 Market Street, Suite 2200
Philadelphia, PA 19103-7013
Telephone: 215-965-1200
Direct Dial: 215-965-1348
Facsimile: 215-965-1210
E-Mail: kbullock@akingump.com

KAB:cmb
7128060